JAMA Psychiatry | Original Investigation

Esketamine Monotherapy in Adults With Treatment-Resistant Depression
A Randomized Clinical Trial

Adam Janik, MD; Xin Qiu, PhD; Rosanne Lane, MAS; Vanina Popova, MD; Wayne C. Drevets, MD; Carla M. Canuso, MD; Matthew Macaluso, DO; Gregory W. Mattingly, MD; Richard C. Shelton, MD; John M. Zajecka, MD; Dong-Jing Fu, MD, PhD

IMPORTANCE Esketamine nasal spray, administered in conjunction with an oral antidepressant, is approved for treatment-resistant depression (TRD). However, the efficacy of esketamine nasal spray administered as monotherapy for patients with TRD has not yet been evaluated.

OBJECTIVE To assess the efficacy and safety of esketamine monotherapy compared to placebo in reducing depressive symptoms in patients with TRD.

DESIGN, SETTING, AND PARTICIPANTS This phase 4, double-blind, placebo-controlled randomized clinical trial was conducted from November 2020 to January 2024 at 51 outpatient centers in the US. Adults with major depressive disorder (*DSM-5* criteria) without psychotic features who experienced inadequate response (≤25% improvement) to 2 or more oral antidepressants during the current depressive episode were eligible for inclusion. Data analyses were conducted from March 1, 2024, to July 8, 2024.

INTERVENTIONS After a 2-week or longer antidepressant-free period, participants were randomized at a 1:1:2 ratio to fixed-dose intranasal esketamine (56 mg or 84 mg) or matching intranasal placebo, administered twice weekly for 4 weeks.

MAIN OUTCOMES AND MEASURES Change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to day 28 (primary efficacy end point) and to 24 hours post–first dose (day 2; key secondary efficacy end point) were analyzed by a mixed-effects model using repeated measures.

RESULTS In this multicenter randomized clinical trial, 378 participants who met prerandomization MADRS severity criteria received 1 or more study drug doses (esketamine, 56 mg [n = 86]; esketamine, 84 mg [n = 95]; or placebo [n = 197]). Mean (SD) participant age was 45.4 (14.1) years, 231 participants (61.1%) were female, and baseline mean (range) MADRS total score was 37.3 (28-50). At day 28, the least-square (LS) mean difference (SE) between esketamine and placebo was −5.1 (1.42) (95% CI, −7.91 to −2.33) for the 56-mg dose and −6.8 (1.38) (95% CI, −9.48 to −4.07) for the 84-mg dose (for each, 2-sided $P < .001$). Observed effect sizes were 0.48 and 0.63 for the 56-mg and 84-mg dose groups, respectively. At day 2 (approximately 24 hours post–first dose), the between-group difference was significant for both esketamine doses: −3.8 (1.29) (95% CI, −6.29 to −1.22; 2-sided $P = .004$) for 56 mg and −3.4 (1.24) (95% CI, −5.89 to −1.00; 2-sided $P = .006$) for 84 mg. The most common treatment-emergent adverse events reported for esketamine (combined doses) were nausea (56 participants [24.8%]), dissociation (55 [24.3%]), dizziness (49 [21.7%]), and headache (43 [19.0%]).

CONCLUSIONS AND RELEVANCE According to results of this multicenter, double-blind randomized clinical trial, esketamine monotherapy may expand treatment options for adult patients with TRD by addressing an unmet need of patients experiencing treatment-limiting tolerability concerns and nonresponse with oral antidepressants.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04599855

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Adam Janik, MD, Department of Neuroscience, Johnson & Johnson, 3210 Merryfield Row, San Diego, CA 92121 (ajanik@its.jnj.com)

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2025.1317
Published online July 2, 2025.

Downloaded from jamanetwork.com by guest on 07/14/2025

Despite the availability of multiple approved antidepressant treatments, major depressive disorder (MDD) continues to be a leading cause of disability[1,2] and to shorten life expectancy.[3] Furthermore, 35% of patients with MDD fail to respond to 2 antidepressant treatment trials,[4] which defines treatment-resistant depression (TRD) according to regulatory agencies.[5,6] This population experiences disproportionate morbidity and mortality, manifesting a 7-fold greater likelihood of attempting suicide[7] and a 3.6-fold higher suicide-specific mortality rate[8] compared to the general population with MDD. Moreover, the longer patients remain unsuccessfully treated, the less likely they are to respond to treatment and the more likely they are to relapse after initial response to a new antidepressant regimen.[9]

Pharmacotherapy for patients with nonresponse to first-line oral antidepressant (OAD) treatment commonly involves augmentation or combination approaches.[10] However, some of these patients encounter tolerability issues (eg, weight gain, sexual dysfunction, lethargy, gastrointestinal issues) with OADs, which significantly contribute to nonadherence or discontinuation.[11-17]

To address the unmet needs of patients with TRD, esketamine nasal spray, an *N*-methyl-D-aspartate receptor antagonist, was evaluated in conjunction with an OAD in phase 2 and 3 studies that demonstrated superior, rapid, and durable antidepressant effects compared to standard of care OADs alone.[18-23] In 2019, the US Food and Drug Administration approved esketamine nasal spray in conjunction with an OAD for patients with TRD.[24] However, to our knowledge, no studies have assessed esketamine's effects as monotherapy without concomitant use of an OAD. The current trial addresses this gap.

Key Points

Question Is esketamine nasal spray used alone (without oral antidepressant) effective in treatment-resistant depression (TRD)?

Findings In the efficacy analysis dataset of this double-blind, multicenter, randomized clinical trial of 378 adults with TRD, both 56-mg and 84-mg doses of esketamine, administered twice weekly, demonstrated statistically significant and clinically meaningful improvement of depressive symptoms vs placebo. Results were initially observed at 24 hours post–first dose and were maintained through day 28 of the double-blind treatment phase.

Meaning These findings support esketamine as a monotherapy option for patients with TRD, especially for those experiencing treatment-limiting tolerability concerns or nonresponse with oral antidepressants.

Methods

The study protocol and amendments were approved by institutional review boards (eMethods 1 in Supplement 2). This study was conducted in accordance with the Good Clinical Practice guideline, assuring the rights, safety, and well-being of study participants were protected, consistent with the ethical principles that originated in the Declaration of Helsinki. All individuals provided written informed consent before entering the study. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Study Population

A full list of inclusion and exclusion criteria is provided in the trial protocol (Supplement 1). The study population and entry criteria are similar to those in the phase 3 TRD studies of esketamine in conjunction with an OAD.[19-23]

Eligible participants were adults aged 18 years or older who had recurrent or single-episode (≥2 years) MDD (via *DSM-5* criteria), without psychotic features, confirmed by the Mini International Neuropsychiatric Interview. At screening, participants were required to have TRD, defined as 25% or less improvement to 2 or more different OADs in the current depressive episode as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire and confirmed in documented records, and to meet a minimum depression severity threshold, established by a total score of 34 or more on the 30-item Inventory of Depressive Symptomatology-Clinician Rated (IDS-C_{30}).

Key exclusion criteria included diagnosis of psychotic disorder, bipolar or related disorders, obsessive-compulsive disorder (current), intellectual disability, autism spectrum disorder, borderline personality disorder, or antisocial personality disorder; current or recent history (past 6 months) of moderate or severe substance or alcohol use disorder; current or recent (past 6 months) suicidal ideation or intent or suicidal behavior within the year prior to screening; positive urine drug screen for specified drugs of abuse; previous treatment with ketamine or esketamine; and nonresponse to electroconvulsive therapy, vagal nerve stimulation, or deep brain stimulation within the current episode.

Study Design

This double-blind, placebo-controlled randomized clinical trial was conducted from November 2020 to January 2024 at 51 US sites. It consisted of 4 phases (eFigure 1 in Supplement 2): (1) 7-week or shorter screening phase during which any current antidepressant and adjunctive antipsychotic treatments, if taken by participants, were tapered and then discontinued for 2 or more weeks before randomization; (2) 4-week double-blind treatment phase; (3) 12-week opt-in open-label phase when participants received esketamine treatment or standard of care OAD and observation; and (4) follow-up approximately 1 week after the final study drug administration.

Double-Blind Treatment Phase (4 Weeks)

Eligible participants were randomized (1:1:2 ratio) to receive double-blind treatment with fixed-dose esketamine nasal spray, 56 mg or 84 mg, or matching placebo nasal spray, which participants self-administered twice weekly for 4 weeks. Dosing and 2 or more hours postdose observation occurred at research sites under direct supervision by site staff.

Two separate randomization lists were generated: (1) the efficacy analysis dataset, including participants who met the predefined site-blinded Montgomery-Åsberg Depression Rating Scale[25] (MADRS) severity criteria (ie, total score ≥28 at

Downloaded from jamanetwork.com by guest on 07/14/2025

screening week 1, week 2, and day 1 [prerandomization] and ≤25% improvement in the MADRS score from screening week 1 to day 1 [prerandomization]), and (2) participants who did not meet these severity criteria. Each computer-generated randomization schedule was stratified by research center and antidepressant treatment status (on or off treatment) at screening, as these variables were considered important prognostic variables to promote a balanced allocation within these strata, and balanced using randomly permuted blocks of 4.

Participants could continue psychotherapy initiated 3 or more months prior to screening. Benzodiazepines were permitted (at a daily dosage equivalent to 6 mg or less of lorazepam), except within 12 hours before study drug dosing.

Open-Label Treatment Phase (12 Weeks)

Participants who completed the double-blind phase and opted into the open-label phase received esketamine, 56 mg, on day 28, regardless of their double-blind study drug/dose assignment. Subsequent doses could be adjusted based on efficacy and tolerability.[24] Use of concomitant medications or interventions during the double-blind and open-label phases is summarized in eMethods 2 in Supplement 2.

Efficacy and Safety Assessments

To minimize the risk of functional unblinding, efficacy assessment (MADRS) raters differed from safety (eg, adverse events, vital signs) assessors.

Site-based assessors rated depressive symptoms using the Structured Interview Guide for the MADRS (SIGMA).[26] Participants rated their depressive symptoms using the 9-item Patient Health Questionnaire[27] (PHQ-9). Investigators rated severity of depressive illness using the Clinical Global Impression–Severity[28] (CGI-S).

Adverse events were monitored throughout the study and vital signs were measured at dosing sessions. The Columbia Suicide Severity Rating Scale[29] (C-SSRS) was used to assess suicidal ideation and behavior at every visit. To evaluate the participant's assessment of study blinding, participants were asked on day 28 (or at early withdrawal from the study) to respond to the question "Which medication did you receive?"

Statistical Analysis

Efficacy Analyses

For the double-blind phase, the efficacy analysis dataset included all randomized participants who received 1 or more doses of study drug and met MADRS-defined severity criteria during screening. The safety analysis dataset included all randomized participants who received 1 or more doses of study drug. The open-label phase dataset included all participants who received 1 or more doses of open-label esketamine.

Analyses were performed using SAS version 9.4 (SAS Institute). The statistical approach for sample size determination and significance level with control for multiplicity are provided in eMethods 3 in Supplement 2.

Primary and Key Secondary Efficacy End Points

The primary efficacy end point, change in MADRS score from baseline to day 28, was analyzed using a mixed-effects model for repeated measures (MMRM) based on observed case data. The model included factors for treatment group (esketamine, 56 mg; esketamine, 84 mg; or placebo), research center, antidepressant treatment status (on or off treatment) at screening, day, day-by-treatment interaction, and baseline MADRS score as a covariate. The within-participant covariance between visits was estimated via an unstructured variance-covariance matrix. Difference in least-square (LS) means and 2-sided 95% confidence intervals were presented for each dose vs placebo. The key secondary efficacy end point, change from baseline in MADRS score at day 2, was analyzed using the same MMRM model described. Comparisons between each dose of esketamine and placebo at day 28 and day 2 were performed using the appropriate contrast. A post hoc analysis using a similar MMRM analysis was conducted for all randomized participants, regardless of MADRS severity criteria (ie, analysis dataset included participants who met the severity criteria and participants who did not meet the severity criteria).

For the primary hypothesis (day 28), if the largest 2-sided *P* value of the 2 esketamine doses vs placebo comparisons was less than .05, both esketamine doses (56 mg and 84 mg) would be declared statistically significantly different from placebo. If the largest *P* value of the primary end point tests had been greater than or equal to .05, the comparison associated with this *P* value would be declared not statistically significant and the smaller *P* value would be compared to the .025 level. The key secondary hypothesis (day 2) was to be tested using the Hochberg procedure only after the null hypothesis for the primary end point was rejected for both doses.

Other Efficacy End Points

The same MMRM model was used to analyze change from baseline in MADRS score at days 8 and 15 and the PHQ-9 score change at days 15 and 28 (with PHQ-9 baseline score as the covariate). Responder (MADRS: ≥50% reduction from baseline; PHQ-9: reduction of ≥6 points or ≥50% improvement from baseline) and remitter (MADRS score ≤10) rates were summarized at each visit. Number needed to treat (NNT) and 95% confidence intervals for response and remission, based on MADRS score, were calculated. Frequency distributions of CGI-S scores (baseline, day 2, day 28) were determined, and change from baseline was summarized. Descriptive statistics of efficacy data also were provided for the open-label phase.

Safety Analyses

Adverse events, serious adverse events, and adverse events leading to discontinuation of study drug were summarized by standardized Medical Dictionary for Regulatory Activities (MedDRA) preferred term, version 26.1. Descriptive statistics were provided for vital signs.

A frequency distribution of C-SSRS scores at each scheduled time point was provided. Shifts from baseline to the most severe postbaseline suicide-related category (no suicidal ideation or behavior [0], suicidal ideation [1-5], suicidal behavior [6-10]) during the double-blind and open-label phases were summarized by treatment group.

Downloaded from jamanetwork.com by guest on 07/14/2025

Results

A total of 378 participants were included in the efficacy analysis dataset, and 476 participants were included in the safety analysis dataset (**Figure 1**). Most participants in the efficacy analysis dataset (358 [94.7%]) and safety analysis dataset (447 [93.9%]) completed double-blind treatment. Following completion of the double-blind phase, 441 participants opted to enter the open-label phase and receive esketamine, 379 (85.9%) of whom completed open-label treatment (median [range] exposure, 78.0 [1-151] days). The final open-label dose was 84 mg for 374 participants (84.8%).

Treatment groups appeared balanced on demographic and baseline clinical characteristics (efficacy analysis: **Table 1**; safety analysis: eTable 1 in Supplement 2). Mean (SD) participant age was 45.4 (14.1) years, 231 participants (61.1%) were female, and baseline mean (range) MADRS total score was 37.3 (28-50). At screening, 248 participants (65.6%) were taking an OAD; 224 participants (59.3%) had failed 2 antidepressants. Lifetime history of suicidal ideation or behavior per screening C-SSRS was reported for 174 participants (46.0%) and 91 participants (24.1%), respectively.

Efficacy

Double-Blind Phase: Efficacy Analysis Dataset

Mean MADRS score decreased (ie, improved) from baseline to day 28 (primary efficacy end point), with greater improvement in each esketamine dose group compared with placebo (**Table 2**). For the 56-mg esketamine group (mean MADRS score at baseline 37.5; mean [SD] change, −12.7 [11.82]) and the 86-mg esketamine group (baseline MADRS score, 36.6; mean [SD] change, −13.9 [11.89]), significantly greater reductions were observed at day 28 vs the placebo group (LS mean difference [SE] vs placebo: −5.1 [1.42] [95% CI, −7.91 to −2.33; $P < .001$] and −6.8 [1.38] [95% CI, −9.48 to −4.07; $P < .001$], respectively). Corresponding effect sizes (Cohen *d*) were 0.48 for 56 mg and 0.63 for 84 mg. Subgroup analyses on the primary end point generally showed that estimates of the between-group differences favored the esketamine groups (eFigure 2 in Supplement 2).

Rapid improvement in depressive symptoms with esketamine, as assessed by the mean (SD) change in MADRS score from baseline, began at approximately 24 hours post-first dose for both the 56-mg group (-13.9 [10.15]) and the 84-mg group (-13.0 [9.68]), with the between-group LS mean difference (SE) vs placebo being significant for each dose group (−3.8 [1.29] [95% CI, −6.29 to −1.22; $P = .004$] and −3.4 [1.24] [95% CI, −5.89 to −1.00; $P = .006$], respectively) (Table 2). **Figure 2** shows the time course of MADRS change during the double-blind phase.

Results of the post hoc analysis of change in MADRS score from baseline to day 28 and to 24 hours post-first dose (primary and key secondary end points, respectively), without regard to screening MADRS severity, were consistent with that of the efficacy analysis dataset and are presented in eTable 2 in Supplement 2.

Response and remission rates were higher in both esketamine groups compared with placebo at all double-blind assessment time points, with response rates approximately 2-fold higher and remission rates 2- to 3-fold higher for each dose group vs placebo at day 28 (eFigure 3 in Supplement 2). The NNT for response at day 28 was 6.5 (95% CI, 1.8-11.3) for esketamine, 56 mg, and 7.1 (95% CI, 1.7-12.5) for esketamine, 84 mg, and for remission, the NNTs were 12.3 (95% CI, −0.4 to 25.0) and 6.7 (95% CI, 2.6-10.9), respectively.

Esketamine-treated participants self-reported improvement in depressive symptoms (eFigure 4 in Supplement 2) and higher response rates (eFigure 5 in Supplement 2) based on PHQ-9 scores.

At baseline, 298 of 377 participants (79.0%) had a CGI-S score of "markedly ill" or higher. At day 28, this decreased to 22 of 82 (26.8%) and 20 of 89 (22.5%) in the 56-mg and 84-mg esketamine groups and 96 of 186 (51.6%) in the placebo group (eFigure 6 in Supplement 2).

Open-Label Phase: Open-Label Analysis Dataset

Depressive symptom improvement, assessed by MADRS score, observed for the esketamine groups during the double-blind phase continued during the open-label phase (eFigure 7 in Supplement 2). For participants who switched from placebo to esketamine after completing the double-blind phase, improvement began at the first open-label assessment and continued thereafter. In general, response and remission rates continued to increase over the open-label phase (eFigure 8 in Supplement 2).

Of the 441 participants receiving esketamine in the open-label phase, 156 (35.4%) received concomitant treatment with OAD, and few received an atypical (18 [4.1%]) or typical (11 [2.5%]) antipsychotic at some point in the open-label phase.

Safety

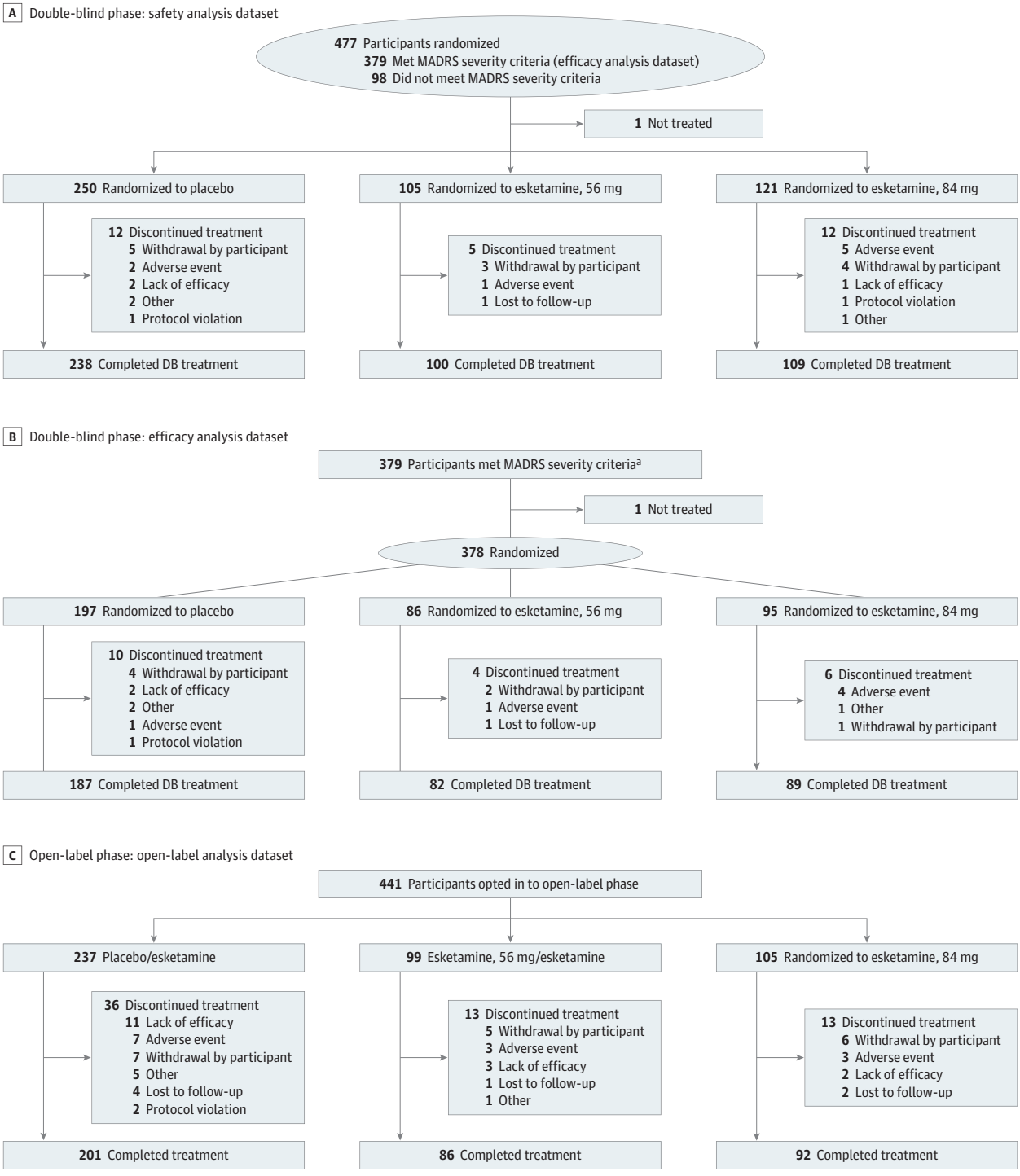
Double-Blind Phase

Treatment-emergent adverse events in the double-blind phase are summarized in eTable 3 in Supplement 2. The most common (incidence >10%) events reported for esketamine-treated participants (combined doses) were nausea (56 of 226 [24.8%] vs 21 of 250 [8.4%] for placebo), dissociation (55 of 226 [24.3%] vs 7 of 250 [2.8%] for placebo), dizziness (49 of 226 [21.7%] vs 18 of 250 [7.2%] for placebo), and headache (43 of 226 [19.0%] vs 22 of 250 [8.8%] for placebo) (**Table 3**). Incidences were similar between the esketamine dose groups (<5% difference for all adverse events sorted by preferred terms). Most adverse events were observed on dosing days (879 of 1032 events [85.2%] in the combined esketamine groups and 257 of 390 events [65.9%] in the placebo group), with most resolving the same day (789 of 879 [89.8%] for the combined esketamine groups and 183 of 257 [71.2%] for the placebo group). Among esketamine-treated participants, 61 of 93 nausea adverse events (65.6%) and 14 of 20 vomiting adverse events (70.0%) occurred during the first 3 dosing sessions (36 of 93 [38.7%] and 12 of 20 [60.0%], respectively, with first-dose administration), and the occurrence of these events attenuated at subsequent dosing sessions.

There were no deaths. Serious adverse events were reported for 1 participant (1.0%) in the 56-mg group (ankle fracture) and 2 participants (1.7%) in the 84-mg group (suicide

Downloaded from jamanetwork.com by guest on 07/14/2025

Figure 1. Disposition of Study Participants



A, Double-blind (DB) phase: safety analysis dataset. B, DB phase: efficacy analysis dataset. C, Open-label phase: open-label analysis dataset. Montgomery-Åsberg Depression Rating Scale (MADRS) severity criteria: MADRS total score ≥28 at screening week 1, week 2, and day 1 (prerandomization) and ≤25% improvement in the MADRS total score from screening week 1 to day 1 (prerandomization). The open-label analysis dataset includes all participants who received ≥1 dose of open-label esketamine. The placebo/esketamine group includes participants who switched from placebo to esketamine after the DB phase.

[a]Included in the safety analysis dataset.

Downloaded from jamanetwork.com by guest on 07/14/2025

Table 1. Summary of Demographics and Baseline Characteristics (Efficacy Analysis Dataset)

Characteristic	No. (%)			
		Esketamine		
	Placebo (n = 197)	56 mg (n = 86)	84 mg (n = 95)	Total (N = 378)
Age, y				
Mean (SD) [range]	45.2 (13.77) [19-73]	46.5 (14.18) [20-75]	44.8 (14.65) [19-76]	45.4 (14.06) [19-76]
≥65	17 (8.6)	10 (11.6)	10 (10.5)	37 (9.8)
Sex				
Female	119 (60.4)	51 (59.3)	61 (64.2)	231 (61.1)
Male	78 (39.6)	35 (40.7)	34 (35.8)	147 (38.9)
Race[a]				
Asian	5 (2.5)	2 (2.3)	4 (4.2)	11 (2.9)
Black or African American	13 (6.6)	4 (4.7)	8 (8.4)	25 (6.6)
White	171 (86.8)	76 (88.4)	81 (85.3)	328 (86.8)
Not reported	3 (1.5)	1 (1.2)	0	4 (1.1)
Other[b]	5 (2.5)	3 (3.5)	2 (2.1)	10 (2.6)
Age at diagnosis of MDD, mean (SD), y	25.9 (11.43)	24.5 (10.54)	25.8 (10.73)	25.5 (11.04)
No. of episodes since diagnosis				
1	36 (18.3)	16 (18.6)	25 (26.3)	77 (20.4)
2	34 (17.3)	16 (18.6)	15 (15.8)	65 (17.2)
≥3	127 (64.5)	54 (62.8)	55 (57.9)	236 (62.4)
Duration current depressive episode, median (range), wk	175.0 (10-1872)	208.0 (12-2555)	208.0 (10-2236)	192.5 (10-2555)
MADRS total score				
Mean (SD) [range]	37.5 (4.90) [28-50]	37.5 (5.23) [28-50]	36.6 (4.48) [29-50]	37.3 (4.88) [28-50]
PHQ-9 total score				
Mean (SD) [range]	19.8 (4.07) [2-27]	20.7 (3.43) [14-27]	19.9 (3.79) [9-27]	20.0 (3.87) [2-27]
IDS-C_{30} total score (at screening)				
Mean (SD) [range]	46.2 (7.21) [34-69]	45.8 (7.00) [34-64]	44.7 (6.90) [34-68]	45.8 (7.10) [34-69]
Antidepressant status at screening or study entry				
On treatment	124 (62.9)	59 (68.6)	65 (68.4)	248 (65.6)
Off treatment	73 (37.1)	27 (31.4)	30 (31.6)	130 (34.4)
Failed antidepressant history[c]				
2	117 (59.4)	49 (57.0)	58 (61.1)	224 (59.3)
≥3	80 (40.6)	37 (43.0)	37 (38.9)	154 (40.7)
History of suicidal ideation in past 6 months[d,e]	105 (53.3)	38 (44.2)	52 (54.7)	195 (51.6)
Lifetime history suicidal behavior[d]	55 (27.9)	19 (22.1)	17 (17.9)	91 (24.1)

Abbreviations: IDS-C_{30}, 30-item Inventory of Depressive Symptomatology–Clinician Rated; MADRS, Montgomery-Åsberg Depression Rating scale; MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire, 9-item.

[a] According to participant self-report.

[b] Includes participants self-reported as multiracial (ie, Asian and White [n = 4]; Black or African American and White [n = 1]; American Indian or Alaska Native and White [n = 1]); Native Hawaiian or Other Pacific Islander (n = 2); American Indian or Alaska Native (n = 1); and unknown race (n = 1).

[c] Failed antidepressant intervention history (defined as ≤25% improvement) taken for ≥6 weeks during the current episode as obtained in the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

[d] Based on screening Columbia Suicide Severity Rating Scale.

[e] History of suicidal behavior within the year prior to screening was an exclusion criterion.

attempt, ophthalmic migraine), with none of these events considered to be related to esketamine by investigators, and for 3 participants (1.2%) in the placebo group (self-injurious ideation, suicidal ideation, and acute myocardial infarction) (eTable 3 in Supplement 2). One participant (1.0%), 5 participants (4.1%), and 3 participants (1.2%) in the respective groups (56 mg, 84 mg, and placebo) discontinued study drug prematurely due to adverse event(s).

There were no unexpected vital sign findings. Mean systolic and diastolic blood pressure values increased at the 40-minute postdose time point and returned close to predose values at 1.5 hours postdose (eFigure 9 in Supplement 2).

There were no unexpected C-SSRS findings. The percentage of participants with no events of suicidal ideation or behavior increased from baseline to day 28 in all groups: from 71 of 105 (67.6%) to 71 of 96 (74.0%) for esketamine, 56 mg; 78 of 121 (64.5%) to 90 of 106 (84.9%) for esketamine, 84 mg; and from 171 of 250 (68.4%) to 177 of 230 (77.0%) for placebo. Treatment-emergent suicidal ideation was reported at least once during the double-blind phase for 7 of 105 participants (6.7%) in the 56-mg esketamine group, 8 of 121 participants (6.6%) in the 84-mg esketamine group, and 24 of 250 participants (9.6%) in the placebo group. Two participants (1 in each esketamine dose group) had suicidal behavior. Consistent with C-SSRS results, few participants reported adverse events potentially related to suicidality (ie, suicide ideation, suicide attempt, or self-injurious ideation) during the double-blind phase (esketamine, 56 mg: 2 par-

Downloaded from jamanetwork.com by guest on 07/14/2025

Table 2. Primary and Secondary End Points: Change in Montgomery-Åsberg Depression Rating Scale Total Score From Baseline to Day 28 and to 24 Hours Post–First Dose (Day 2)[a]

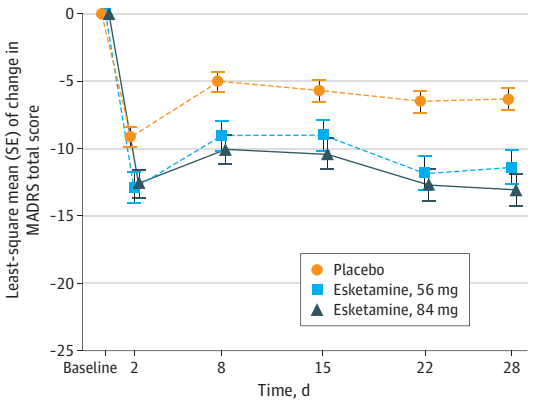
	Placebo	Esketamine	
		56 mg	84 mg
Baseline			
No.	197	86	95
Mean (SD) [range]	37.5 (4.90) [28 to 50]	37.5 (5.23) [28 to 50]	36.6 (4.48) [29 to 50]
Primary end point			
No. at day 28	185	82	89
Mean (SD) change from baseline to day 28	−7.0 (10.07)	−12.7 (11.82)	−13.9 (11.89)
MMRM analysis[b]			
Difference of LS means (SE) [95% CI on difference]	NA	−5.1 (1.42) [−7.91 to −2.33]	−6.8 (1.38) [−9.48 to −4.07]
2-Sided *P* value	NA	<.001	<.001
Key secondary end point			
No. at day 2	195	84	93
Mean (SD) change from baseline to day 2	−9.7 (10.27)	−13.9 (10.15)	−13.0 (9.68)
MMRM analysis[b]			
Difference of LS means (SE) [95% CI on difference]	NA	−3.8 (1.29) [−6.29 to −1.22]	−3.4 (1.24) [−5.89 to −1.00]
2-Sided *P* value	NA	.004	.006

Abbreviations: LS, least squares; MADRS, Montgomery-Åsberg Depression Rating scale; MMRM, mixed model for repeated measures; NA, not applicable.

[a] MADRS total score ranges from 0-60; a higher score indicates a more severe condition. Negative change in score indicates improvement. Negative difference favors esketamine.

[b] Based on MMRM with change from baseline as the response variable, fixed-effect model terms including treatment group (placebo; esketamine, 56 mg; esketamine, 84 mg), research center, antidepressant treatment status (on or off treatment) at screening, day, and day-by-treatment interaction, and the baseline MADRS total score as a covariate.

Figure 2. Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score: Change Over Time in the Double-Blind Phase



No. of participants

Placebo	197	195	190	189	187	185
Esketamine, 56 mg	86	84	84	84	81	82
Esketamine, 84 mg	95	93	89	89	87	89

MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement. Least-square mean and SE were based on mixed model for repeated measures, with change from baseline as the response variable and the fixed-effect model terms for intervention group (placebo; esketamine, 56 mg; esketamine, 84 mg), analysis center, antidepressant treatment status (on or off treatment) at screening entry, day, and day-by-treatment interaction, and the baseline MADRS total score as a covariate.

ticipants [1.9%]; esketamine, 84 mg: 3 participants [2.5%]; placebo: 3 participants [1.2%]).

Responding to the question, "Which medication did you receive?" on day 28, 90 of 192 participants in the placebo group (46.9%) strongly believed they had received placebo, and of esketamine-treated participants, 59 of 83 in the 56-mg group (71.1%) and 72 of 92 in the 84-mg group (78.3%) strongly believed they had received esketamine.

Open-Label Phase

There were no deaths. Adverse events reported during the open-label phase are summarized in Table 3, serious adverse events are reported in eTables 3 and 4 in Supplement 2, and discontinuations due to adverse events are reported in eTables 3 and 5 in Supplement 2. Adverse events (Table 3) and C-SSRS results (eResults in Supplement 2) for esketamine-treated patients during the open-label phase were consistent with those in the double-blind phase.

Discussion

In this first placebo-controlled, monotherapy randomized clinical trial, esketamine demonstrated rapid and robust efficacy at both 56- and 84-mg doses, with a clinically meaningful and statistically significant treatment effect, initially observed 24 hours after the first dose, representing substantial benefit compared to OADs, which typically exhibit a delayed onset of effect.[30] The antidepressant effect was maintained through day 28 of the double-blind phase. Notably, effect size for the primary efficacy end point of 0.48 (56 mg) and 0.63 (84 mg) supports robust efficacy of esketamine monotherapy in a TRD population. The treatment difference for both esketamine doses at days 2 and 28 exceeded the 2-point difference in MADRS score vs placebo established as clinically meaningful.[31,32] The study had an unique design feature, which used the IDS-C_{30} as an entry criterion for depression severity and used the site-blinded MADRS severity criteria to define the efficacy analysis dataset. This design fea-

Downloaded from jamanetwork.com by guest on 07/14/2025

Table 3. Most Common Treatment-Emergent Adverse Events Reported

	No. (%) of participants			
		Esketamine		
Adverse event[a]	Placebo (n = 250)	56 mg (n = 105)	84 mg (n = 121)	Doses combined (n = 226)
Double-blind treatment phase				
Participants with ≥1 adverse event(s)	123 (49.2)	76 (72.4)	91 (75.2)	167 (73.9)
Most frequently reported adverse events[b]				
Nausea	21 (8.4)	24 (22.9)	32 (26.4)	56 (24.8)
Dissociation	7 (2.8)	23 (21.9)	32 (26.4)	55 (24.3)
Dizziness	18 (7.2)	22 (21.0)	27 (22.3)	49 (21.7)
Headache	22 (8.8)	19 (18.1)	24 (19.8)	43 (19.0)
Feeling drunk	2 (0.8)	8 (7.6)	8 (6.6)	16 (7.1)
Anxiety	3 (1.2)	5 (4.8)	10 (8.3)	15 (6.6)
Fatigue	11 (4.4)	8 (7.6)	7 (5.8)	15 (6.6)
Vomiting	1 (0.4)	5 (4.8)	10 (8.3)	15 (6.6)
Insomnia	9 (3.6)	6 (5.7)	5 (4.1)	11 (4.9)
Somnolence	4 (1.6)	6 (5.7)	3 (2.5)	9 (4.0)
Adverse event[a]	Placebo/esketamine (n = 237)	Esketamine, 56 mg/esketamine (n = 99)	Esketamine, 84 mg/esketamine (n = 105)	Total (N = 441)
Open-label treatment phase				
Participants with ≥1 adverse event(s)	174 (73.4)	64 (64.6)	67 (63.8)	305 (69.2)
Most frequently reported adverse events[b]				
Nausea	69 (29.1)	18 (18.2)	15 (14.3)	102 (23.1)
Dissociation	42 (17.7)	12 (12.1)	15 (14.3)	69 (15.6)
Dizziness	45 (19.0)	8 (8.1)	10 (9.5)	63 (14.3)
Headache	36 (15.2)	13 (13.1)	11 (10.5)	60 (13.6)
Vomiting	28 (11.8)	6 (6.1)	2 (1.9)	36 (8.2)
Fatigue	18 (7.6)	6 (6.1)	5 (4.8)	29 (6.6)
Feeling drunk	13 (5.5)	6 (6.1)	6 (5.7)	25 (5.7)
Diarrhea	16 (6.8)	5 (5.1)	3 (2.9)	24 (5.4)
Dysgeusia	14 (5.9)	4 (4.0)	5 (4.8)	23 (5.2)
Anxiety	14 (5.9)	3 (3.0)	4 (3.8)	21 (4.8)
Hypesthesia	15 (6.3)	2 (2.0)	4 (3.8)	21 (4.8)
Throat irritation	13 (5.5)	2 (2.0)	2 (1.9)	17 (3.9)
Upper respiratory tract infection	12 (5.1)	0	1 (1.0)	13 (2.9)

[a] Adverse events in the double-blind phase are reported in descending order of incidence in the combined esketamine 56 mg and 84 mg groups and in alphabetical order for events with identical incidence. Adverse events in the open-label phase are summarized for the open-label analysis dataset, which includes all participants who received ≥1 dose(s) of open-label esketamine. The placebo/esketamine group includes participants who switched from placebo to esketamine after the double-blind phase. Adverse events are reported in descending order of incidence in the total group and in alphabetical order for events with identical incidence.

[b] ≥5% of Participants in any treatment group.

ture was aimed to prevent potential inflation of baseline MADRS score, which in turn would increase the sensitivity of signal detection for the treatment effect.[33] Notably, the results of the primary and key secondary end points from the efficacy analysis dataset were consistent with those from the dataset that included all randomized participants, regardless of meeting MADRS severity criteria. In participants who continued esketamine in the 12-week, single-arm, open-label phase, depressive symptoms remained stable or improved. These findings are consistent with and expand upon efficacy findings in a subgroup of SUSTAIN-3 patients (n = 50) who received esketamine monotherapy for 3 or more months.[34]

Response and remission rates were higher in both esketamine groups vs placebo at all double-blind time points. The NNTs with esketamine monotherapy for response (6.5 [56 mg] and 7.1 [84 mg]) and remission (12.3 [56 mg] and 6.7 [84 mg]) after 4-week treatment align with NNTs from phase 3 studies of adjunctive esketamine treatment of TRD.[35]

There were no unexpected tolerability findings. Most adverse events commonly observed with esketamine treatment were mild or moderate in severity and transient in duration, occurring on a dosing day and resolving during the 2-hour postdosing, in-clinic observation period. No esketamine-treated participant experienced a treatment-related serious adverse event, and few discontinued esketamine due to an adverse event. The latter findings are noteworthy given the relatively high rates of drug-related adverse events, nonadherence, and early discontinuation due to tolerability issues among patients with MDD treated with OADs.[11,14,16,17]

Downloaded from jamanetwork.com by guest on 07/14/2025

Incidences of treatment-emergent suicidal ideation (based on C-SSRS) appear similar to incidences observed in short-term studies of adjunctive esketamine in TRD (10.4% [esketamine, 56 mg]; 7.1% [esketamine, 84 mg] vs placebo [11.5%] in TRANSFORM-1; 5.4% [esketamine] vs 6.4% [placebo] in TRANSFORM-2).[20,22] Taken together, the safety profile of esketamine in this monotherapy study is consistent with its safety profile demonstrated in adjunctive treatment trials.[18-23]

Limitations

Exclusion of patients with significant psychiatric or medical comorbidities or substance dependence, as well as limited racial and ethnic diversity among participants, may lessen the generalizability of our findings. The patient population, study design, and efficacy scales were, however, aligned with the adjunctive phase 3 TRD registration studies,[19-23] allowing confirmation that esketamine monotherapy would be an effective and safe treatment for the same population, without an OAD. Another limitation is that adverse events more commonly associated with esketamine than placebo (eg, dissociation, dizziness) may have led to functional unblinding of some participants. To minimize this risk due to well-characterized transient effects associated with esketamine, the study design required that site raters who performed efficacy assessments differed from those who performed safety assessments. Lastly, the open-label phase was single arm, without a control arm, and thus the results were exploratory in nature.

At day 28, three-fourths of esketamine-treated participants strongly believed they had received esketamine. By way of comparison, in a meta-analysis of randomized, controlled clinical trials of depressive disorder, the proportion of patients who correctly guessed which treatment they received (antidepressant [SSRI, SNRI] or placebo) ranged from 45% to 71%.[36] To evaluate the impact of psychomimetic effect of esketamine on the efficacy results, Williams and colleagues[37] performed a post hoc analysis of the relationship between dissociation and esketamine response. Similar response rates were observed in esketamine-treated participants with and without an adverse event of dissociation: 31.6% vs 30.4%, respectively, in the 56-mg group and 30.3% vs 27.8% in the 84-mg group. Moreover, prior analyses showed that esketamine's antidepressant effects are similar in patients who experience dissociation-related adverse events vs those who do not.[38] Taken together, the lack of relationship between esketamine response and dissociation suggests that the potentially unblinding psychotomimetic effect of esketamine does not account for the efficacy observed in participants receiving esketamine. Further, in a longitudinal study of 1148 participants with TRD who responded to esketamine for up to 6.5 years, persistence of antidepressant efficacy in most participants would not likely be explained by a placebo effect attributable to functional unblinding, given the relatively transient nature of placebo responses in MDD.[39,40]

Conclusions

Results from this study strengthen the body of evidence for esketamine's antidepressant efficacy and inform on the monotherapy treatment option for patients with TRD, particularly when OADs have inadequate efficacy but high adverse effect burden. That the 84-mg dose, the most common in real-world practice,[41,42] conferred a larger effect size without safety concerns supports the potential for starting esketamine monotherapy at this dose.

In the context of well-characterized treatment-limiting tolerability concerns and limited efficacy of OADs for some patients, as well as well-known noncompliance in patients with MDD, this study supports esketamine monotherapy as an important option in the management of patients for whom OADs or other pharmacological treatments are no longer appropriate or acceptable. Esketamine monotherapy can potentially address a significant unmet need for the especially vulnerable untreated TRD subpopulation at risk of serious outcomes.

ARTICLE INFORMATION

Accepted for Publication: March 22, 2025.

Published Online: July 2, 2025. doi:10.1001/jamapsychiatry.2025.1317

Open Access: This is an open access article distributed under the terms of the CC-BY-NC-ND License, which does not permit alteration or commercial use, including those for text and data mining, AI training, and similar technologies. © 2025 Janik A et al. *JAMA Psychiatry*.

Author Affiliations: Department of Neuroscience, Johnson & Johnson, San Diego, California (Janik, Drevets); Department of Clinical Biostatistics, Johnson & Johnson, Titusville, New Jersey (Qiu, Lane); Department of Neuroscience, Johnson & Johnson, Beerse, Belgium (Popova); Department of Neuroscience, Johnson & Johnson, Titusville, New Jersey (Canuso, Fu); Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham (Macaluso); Midwest Research Group–St Charles Psychiatric Associates, St Charles, Missouri (Mattingly); Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham School of Medicine, Huntsville Regional Medical Campus, Huntsville (Shelton); Department of Psychiatry, Rush University, Chicago, Illinois (Zajecka).

Author Contributions: Drs Janik and Fu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Janik, Lane, Popova, Drevets, Canuso.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Janik, Fu.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Qiu, Lane.
Supervision: Janik, Popova, Drevets, Canuso, Fu.

Conflict of Interest Disclosures: Drs Janik, Qiu, Popova, Drevets, Canuso, and Fu and Ms Lane are employees of Johnson & Johnson, and all are stockholders of Johnson & Johnson. Drs Janik, Popova, Drevets, Canuso, and Fu report holding a patent for esketamine for treatment of depression, the rights of which were assigned to Johnson & Johnson. Dr Macaluso reported receiving grant support for research from Alto, Autobahn, Boehringer Ingelheim, Janssen, LivaNova, Merck, Neurocrine, the US National Institutes of Health (NIH)/National Institute of Mental Health (NIMH), Otsuka, the Patient-Centered Outcomes Research Institute (PCORI), and Supernus/Navitor (all clinical trial payments made to the University of Alabama at Birmingham); providing consultancy to edYOU, EmbodyXR, Intra-Cellular Therapies Inc, LivaNova, NuSachi Labs, PharmaTher, Residents Medical, Tactical Mind Solutions, and the University of Missouri; receiving personal fees from Alfa Sigma, edYOU, and LivaNova; receiving nonfinancial support from electroCore for an investigator-initiated trial; holding a patent for intravenous ketamine for amyotrophic lateral sclerosis (held under his and other faculty members' names by University of Kansas School of Medicine); serving on Janssen's speakers bureau for esketamine from April 2019 to June 2020; and receiving royalties from Springer Nature and the American Psychiatric Association Publishing (for textbooks published). Dr Mattingly reported

Downloaded from jamanetwork.com by guest on 07/14/2025

receiving grant support for research from AbbVie, Acadia, Akilli, Alkermes, Alto Therapeutics, Autobahn, Avanir, Axsome, Boehringer Ingelheim, Cingulate, Click Therapeutics, Compass, Corium, Emalex, Idorsia, Intra-Cellular Therapies Inc, Johnson & Johnson Innovative Medicine, Karuna, Lumos Labs, Medgenics, Neumora, Neurocrine, NLS Pharma, Otsuka, Redax, Relmada, Roche, Sage, Sirtsei, Sumitomo, Sunovion, Supernus, Takeda, and Teva; providing consultancy to AbbVie, Acadia, Akilli, Alkermes, Angelini, Axsome, Aytu, Biogen, Boehringer Ingelheim, Cerevel, Corium, Eisai, Ironshore, Intra-Cellular Therapies Inc, Janssen, LivaNova, Lumos Labs, Lundbeck, Manus, Neurocrine, Noven, Otsuka, Redax, Relmada, Revibe, Roche, Sage, Sirona, Sky Therapeutics, Sunovion, Supernus, Takeda, Teva, and Tris Pharma; and serving on the speakers bureau for AbbVie, Alkermes, Angelini, Axsome, Corium, Intra-Cellular Therapies Inc, Ironshore, Janssen, Lundbeck, Luye, Neurocrine, Noven, Otsuka, Sunovion, Supernus, Takeda, Teva, and Tris Pharma. Dr Shelton reported receiving grant support for research from AbbVie, Alto Pharmaceuticals, Boehringer Ingelheim, Denovo Biopharma, Gate Neuroscience, INmune Bio, Intra-Cellular Therapies Inc, Johnson & Johnson Innovative Medicine, LivaNova PLC, NIMH, Navitor Pharmaceuticals, Neumora, Neurocrine Biosciences, NeuroRx, the NIH, Novartis AG, NRx Pharmaceuticals, Otsuka Pharmaceuticals, PCORI, Sumitomo Pharma America, and Supernus Pharmaceuticals; providing consultancy to Boehringer Ingelheim, Denovo Biopharma, EQUULUS Therapeutics, Evecxia Therapeutics, Johnson & Johnson Innovative Medicine, NeuroRx, Novartis AG, Otsuka Pharmaceuticals, Seelos Therapeutics, Sumitomo Pharma America, and Supernus Pharmaceuticals; and receiving royalties from Springer Nature Group and Wolters-Kluwer NV. Dr Zajecka reported receiving grant support for research from Abbott, Axsome, Boehringer Ingelheim, the Cheryl T. Herman Foundation, COMPASS Pathfinder Limited, Cybin IRL Limited, ElMindA, Hoffman-LaRoche, Johnson & Johnson/Janssen, LivaNova, Neurocrine, Novartis, Otsuka, Praxis, SAGE Therapeutics, and Takeda and providing consultancy to/advisory board participation for Alpha Sigma, ElMindA, Johnson & Johnson/Janssen, and Paragon. No other disclosures were reported.

Funding/Support: The study was funded by Janssen Research & Development.

Role of the Funder/Sponsor: Employees of the sponsor were involved in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: This paper was presented as a poster at the 2024 meeting of the American Society of Clinical Psychopharmacology; May 28-31, 2024; Miami, Florida; at the 37th European College of Neuropsychopharmacology Congress; September 21-24, 2024; Milan, Italy; and at the 63rd Annual Meeting of the American College of Neuropsychopharmacology; December 8-11, 2024; Phoenix, Arizona.

Data Sharing Statement: See Supplement 3.

Additional Contributions: The authors acknowledge Jaskaran B. Singh, MD, who contributed to the design of the study during his employment at Johnson & Johnson. Sandra Norris, PharmD, MBA (Norris Communications Group), supported by Janssen Research & Development, a Johnson & Johnson company, provided writing assistance, and Ellen Baum, PhD (Johnson & Johnson), provided additional editorial support. The authors thank the study participants, without whom this study would never have been accomplished, and all the investigators for their participation in this study.

REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204-1222. doi:10.1016/S0140-6736(20)30925-9

2. World Health Organization. Depression and other common mental disorders: global health estimates. Accessed October 28, 2024. https://www.who.int/publications/i/item/depression-global-health-estimates

3. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72(4):334-341. doi:10.1001/jamapsychiatry.2014.2502

4. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917. doi:10.1176/ajp.2006.163.11.1905

5. Center for Drug Evaluation and Research, US Food and Drug Administration. Major depressive disorder: developing drugs for treatment. Accessed October 28, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/major-depressive-disorder-developing-drugs-treatment

6. European Medicines Agency. Clinical investigation of medicinal products in the treatment of depression –Scientific guideline. Accessed October 28, 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-depression-revision-2_en.pdf

7. Feldman RL, Dunner DL, Muller JS, Stone DA. Medicare patient experience with vagus nerve stimulation for treatment-resistant depression. *J Med Econ*. 2013;16(1):62-74. doi:10.3111/13696998.2012.724745

8. Kern DM, Canuso CM, Daly E, et al. Suicide-specific mortality among patients with treatment-resistant major depressive disorder, major depressive disorder with prior suicidal ideation or suicide attempts, or major depressive disorder alone. *Brain Behav*. 2023;13(8):e3171. doi:10.1002/brb3.3171

9. Rush AJ. STAR*D: what have we learned? *Am J Psychiatry*. 2007;164(2):201-204. doi:10.1176/ajp.2007.164.2.201

10. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Accessed October 28, 2024. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf

11. Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. *Psychother Psychosom*. 2016;85(5):270-288. doi:10.1159/000447034

12. Coe A, Gunn J, Fletcher S, Murray E, Kaylor-Hughes C. Self-reported reasons for reducing or stopping antidepressant medications in primary care: thematic analysis of the *diamond* longitudinal study. *Prim Health Care Res Dev*. 2023;24:e16. doi:10.1017/S1463423623000038

13. Bull SA, Hunkeler EM, Lee JY, et al. Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother*. 2002;36(4):578-584. doi:10.1345/aph.1A254

14. Golder S, Medaglio D, O'Connor K, Hennessy S, Gross R, Gonzalez Hernandez G. Reasons for discontinuation or change of selective serotonin reuptake inhibitors in online drug reviews. *JAMA Netw Open*. 2023;6(7):e2323746. doi:10.1001/jamanetworkopen.2023.23746

15. Kelly K, Posternak M, Alpert JE. Toward achieving optimal response: understanding and managing antidepressant side effects. *Dialogues Clin Neurosci*. 2008;10(4):409-418. doi:10.31887/DCNS.2008.10.4/kkelly

16. Olfson M, Marcus SC, Tedeschi M, Wan GJ. Continuity of antidepressant treatment for adults with depression in the United States. *Am J Psychiatry*. 2006;163(1):101-108. doi:10.1176/appi.ajp.163.1.101

17. Serna MC, Cruz I, Real J, Gascó E, Galván L. Duration and adherence of antidepressant treatment (2003 to 2007) based on prescription database. *Eur Psychiatry*. 2010;25(4):206-213. doi:10.1016/j.eurpsy.2009.07.012

18. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2018;75(2):139-148. doi:10.1001/jamapsychiatry.2017.3739

19. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2019;76(9):893-903. doi:10.1001/jamapsychiatry.2019.1189

20. Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *Int J Neuropsychopharmacol*. 2019;22(10):616-630. doi:10.1093/ijnp/pyz039

21. Ochs-Ross R, Daly EJ, Zhang Y, et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression-TRANSFORM-3. *Am J Geriatr Psychiatry*. 2020;28(2):121-141. doi:10.1016/j.jagp.2019.10.008

22. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *Am J Psychiatry*. 2019;176(6):428-438. doi:10.1176/appi.ajp.2019.19020172

23. Wajs E, Aluisio L, Holder R, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study

Downloaded from jamanetwork.com by guest on 07/14/2025

(SUSTAIN-2). *J Clin Psychiatry*. 2020;81(3):19m12891. doi:10.4088/JCP.19m12891

24. Spravato® (esketamine) nasal spray. Prescribing information. Janssen Pharmaceutical Companies; 2023. Accessed October 28, 2024. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf

25. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389. doi:10.1192/bjp.134.4.382

26. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). *Br J Psychiatry*. 2008;192(1):52-58. doi:10.1192/bjp.bp.106.032532

27. Spitzer RL, Kroenke K, Williams JB; Primary Care Evaluation of Mental Disorders. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. primary care evaluation of mental disorders. Patient Health Questionnaire. *JAMA*. 1999;282(18):1737-1744. doi:10.1001/jama.282.18.1737

28. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education, and Welfare; 1976.

29. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164(7):1035-1043. doi:10.1176/ajp.2007.164.7.1035

30. Machado-Vieira R, Baumann J, Wheeler-Castillo C, et al. The timing of antidepressant effects: a comparison of diverse pharmacological and somatic treatments. *Pharmaceuticals (Basel)*. 2010;3(1):19-41. doi:10.3390/ph3010019

31. Melander H, Salmonson T, Abadie E, van Zwieten-Boot B. A regulatory apologia–a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. *Eur Neuropsychopharmacol*. 2008;18(9):623-627. doi:10.1016/j.euroneuro.2008.06.003

32. Montgomery SA, Möller HJ. Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? *Int Clin Psychopharmacol*. 2009;24(3):111-118. doi:10.1097/YIC.0b013e32832a8eb2

33. Fava M. How should we design future mechanistic and/or efficacy clinical trials? *Neuropsychopharmacology*. 2024;49(1):197-204. doi:10.1038/s41386-023-01600-9

34. Fu DJ, Lopena O, Quach P, Zaki N, Sun L. A post hoc analysis of patients who received esketamine nasal spray monotherapy in an open-label safety extension study (SUSTAIN-3) (abstract TH29). Abstract presented at: American Society of Clinical Psychopharmacology (ASCP) Annual Meeting; May 31-June 3, 2022; Scottsdale, Arizona. Accessed October 28, 2024. https://pmg.joynadmin.org/documents/1005/628e68149557aa5a02655c33.pdf

35. Citrome L, DiBernardo A, Singh J. Appraising esketamine nasal spray for the management of treatment-resistant depression in adults: number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Affect Disord*. 2020;271:228-238. doi:10.1016/j.jad.2020.03.106

36. Lin YH, Sahker E, Shinohara K, et al. Assessment of blinding in randomized controlled trials of antidepressants for depressive disorders 2000-2020: a systematic review and meta-analysis. *EClinicalMedicine*. 2022;50:101505. doi:10.1016/j.eclinm.2022.101505

37. Williams D, Fu DJ, Bossie C, Qiu X, Bangerter A, Canuso C. Evaluating the relationship between esketamine monotherapy efficacy and dissociation in patients with treatment-resistant depression. Paper presented at: 21st annual meeting of the International Society for CNS Clinical Trials and Methodology (ISCTM); February 19-21, 2025; Washington, DC

38. Chen G, Chen L, Zhang Y, et al. Relationship between dissociation and antidepressant effects of esketamine nasal spray in patients with treatment-resistant depression. *Int J Neuropsychopharmacol*. 2022;25(4):269-279. doi:10.1093/ijnp/pyab084

39. Khan A, Mar KF, Brown WA. Consistently modest antidepressant effects in clinical trials: the role of regulatory requirements. *Psychopharmacol Bull*. 2021;51(3):79-108.

40. Zaki N, Chen LN, Lane R, et al. Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression: interim results of the SUSTAIN-3 study. *Neuropsychopharmacology*. 2023;48(8):1225-1233. doi:10.1038/s41386-023-01577-5

41. Joshi K, Pilon D, Shah A, Holiday C, Karkare S, Zhdanava M. Treatment patterns, healthcare utilization, and costs of patients with treatment-resistant depression initiated on esketamine intranasal spray and covered by US commercial health plans. *J Med Econ*. 2023;26(1):422-429. doi:10.1080/13696998.2023.2188845

42. Teeple A, Zhdanava M, Pilon D, Caron-Lapointe G, Lefebvre P, Joshi K. Access and real-world use patterns of esketamine nasal spray among patients with treatment-resistant depression covered by private or public insurance. *Curr Med Res Opin*. 2023;39(8):1167-1174. doi:10.1080/03007995.2023.2239045

Downloaded from jamanetwork.com by guest on 07/14/2025